REMARKS

Claims 69-73, 102, 108-110 and 115-122 are pending in this application.

Applicants request entry of the amendments submitted with their November 12, 2004 Reply.

Applicants have canceled claims 106 and 112-114 without prejudice or waiver of applicants' right to file for and obtain claims directed to any canceled subject matter in future divisional or continuing applications claiming priority from this application.

Applicants have amended claim 69 to specify that the morphogenic protein is OP-1.

Applicants have amended claims 108-110, 116-118, 120 and 121 to replace the term "morphogenic protein" with the term "OP-1" to parallel its antecedent basis.

None of the amendments introduces new matter.

Applicants now address the Examiner's December 15, 2004 Advisory Action below:

New Issues

The Examiner states that the proposed amendments in applicants' November 12, 2004 Reply will not be entered because they raise new issues that would require further consideration and/or search. The Examiner states that the amendment further restricts the scope of the claim and would necessitate a further consideration of the other members of the Markush group of morphogenic proteins.

Applicants request entry and consideration of the amendments submitted in applicants' November 12, 2004 Reply with the request for continued examination of this application.

35 U.S.C. § 103(a)

The Examiner states that applicants' arguments presented in their November 12, 2004 Reply are directed to the newly proposed amended claims and that amendment has not been entered.

The Examiner states that applicants' "obvious to try" argument does not speak to the obviousness of combining a BMP and heparin. The Examiner further states that the teachings of Wang,

U.S. Patent 5,166,058 ("Wang"), Kuberasampath, U.S. Patent 5,674,844 ("Kuberasampath II") and Reddi, A. H. et al., "Bone induction by osteogenin and bone morpohogenic proteins," Biomaterials, 11: pp. 33-34 (1990) ("Reddi") lead to a general expectation of greater than additive osteogenic effects when using mixtures of a BMP and IGF-I.

First, applicants request entry of the amendments submitted in applicants' November 12, 2004 Reply with the request for continued examination of this application.

Second, applicants traverse the Examiner's rejections. However, to expedite prosecution, applicants have amended the claims to recite a method for inducing tissue formation comprising the step of implanting a morphogenic device comprising OP-1, a MPSF selected from IGF-I, hydrocortisone, insulin and parathyroid hormone, wherein the OP-1 and MPSF act synergistically to induce tissue formation. Applicants have demonstrated that IGF-I, hydrocortisone, insulin and PTH unexpectedly synergistically stimulate OP-1 to induce tissue formation.

Wang discloses the use of BMP-2 and BMP-4 with the growth factor IGF-I for treating bone, cartilage, periodontal diseases, wound healing and tissue repair. Wang does not teach or suggest the use of OP-1 with IGF-I to synergistically induce tissue formation as claimed in the instant application. Furthermore, nothing in Wang teaches or suggests that hydrocortisone, insulin or parathyroid hormone can synergize the tissue inductive ability of OP-1.

Kuberasampath II discloses a method for stimulating bone formation using BMPs and that the BMPs may be administered with cofactors known to have a "beneficial effect" on bone modeling, such as PTH, vitamin D3, prostaglandins, dexamethasone, IGF-I and IGF-II. Kuberasampath II does not teach or suggest that the cofactors and BMPs act synergistically to induce tissue formation.

Similarly, Reddi discloses the general idea that the initiation of bone induction by BMPs may be promoted by PDGF, TGF-β, IGF-I, IGF-II and FGF. Like Kuberasampath II, Reddi does not teach or suggest that OP-1 and IGF-I synergistically induce tissue formation. Therefore, nothing in the combination of Wang,

Kuberasampath II and Reddi would provide the skilled worker in the art with a reasonable expectation that IGF-I, hydrocortisone, insulin and parathyroid hormone would synergistically stimulate the ability of OP-1 to induce tissue formation, as recited in the amended claims of the instant application.

With respect to the obviousness of the claims reciting heparin as a carrier, the basis for novelty and nonobviousness of those claims is the same as that for the other claims, i.e., the use of IGF-I, hydrocortisone, insulin and PTH to synergistically stimulate the ability of OP-1 to induce tissue formation. Accordingly, for all the above reasons, applicants request that the Examiner withdraw the obviousness rejection.

35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection under 35 U.S.C. § 112, first paragraph. The Examiner states that the references provided by applicants only indicate that induction of AP activity may be used to assess *in vitro* osteogenic activity and none of these references indicate that the synergistic enhancement of AP activity is predictive of synergistic enhancement of bone, cartilage, tendon/ligament and neural tissue

in vivo. The Examiner further states that Li et al., "Osteogenic potential of five different recombinant human bone morphogenetic protein adenoviral vectors in the rat," Gene Ther, 10: pp. 1735-1743 (2003) ("Li") discloses that BMP-9 is one of the most osteogenic BMPs in rat models of bone formation but that although previous studies have shown that AP expression is a consistent *in vitro* osteogenic response seen in BMP-responsive cells and usually correlates with the ability of the various BMPs to induce bone formation *in vivo*, it may not accurately predict *in vivo* osteogenic potential. Applicants traverse.

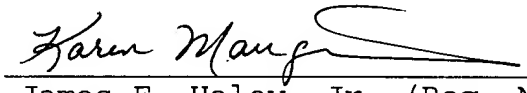
However, to expedite prosecution, applicants have amended the claims to specify that the morphogenic protein is OP-1. Applicants respectfully submit that contrary to the Examiner's contention, applicants have clearly demonstrated that AP activity *in vitro* does correlate with the induction of bone *in vivo* (see e.g., Yeh et al., "Osteogenic protein-1 (OP-1, BMP-7) induces osteoblastic cell differentiation of the pluripotent mesenchymal cell line C2C12", J Cell Biochem, 87: pp. 292-304 (2002); Ripamonti et al., "Long-term evaluation of bone formation by osteogenic protein 1 in the baboon and relative efficacy of bone-derived bone morphogenic proteins delivered by irradiated

xenogeneic collagenous matrices", J Bone Miner Res, 15: pp. 1798-1809 (2000); both of which were submitted with applicants' November 12, 2004 Reply). Applicants have demonstrated such a nexus by providing the Examiner with ample support from publications that the AP activity of OP-1 is correlated with *in vivo* bone inductive activity. In fact, OP-1 is an FDA approved product currently being used in clinical settings for recalcitrant long bone nonunions and revision spinal fusions. Accordingly, there is a nexus between OP-1 induced AP activity *in vitro* and OP-1 induced bone formation *in vivo*. Applicants therefore request that the Examiner withdraw this rejection.

CONCLUSION

In view of the above, applicants respectfully request consideration and early allowance of the pending claims in this application.

Respectfully submitted,



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